REMARKS

Reconsideration of this application is respectfully requested in view of the previous amendments and the following remarks.

Claims 1-10 and 12-20 are currently in this case. Claims 1-6, 9, 14, 16, 17, and 20 have been amended. No new matter has been added.

The Examiner rejected different but overlapping sets of claims on several grounds: obviousness-type double-patenting, failure to particularly point out and distinctly claim the subject matter of the invention, anticipation under 35 U.S.C. 102(b), and obviousness under 35 U.S.C. § 103(a). As a result, all claims in this case have been rejected. The Applicants respectfully traverse each ground for the rejection.

The claims of the instant application are drawn to microbubbles for ultrasonic imaging. The microbubbles according to the present invention comprise at least one fluorocarbon gas and at least one modifier gas in a certain molar ratio (between about 100:1 and about 1:1000). The microbubbles further comprise a membrane surrounding the gas mixture, wherein the membrane is preferably formed of surfactant. The microbubbles grow and shrink to maintain osmotic equilibrium with the physiological gas saturation of the surrounding external medium. The microbubbles of the present invention maintain an internal osmotic pressure that is capable of counteracting the Laplace pressure produced by the surface membrane surrounding the microbubble, thus stabilizing the microbubble.

Rejection under obviousness-type double-patenting.

The Examiner has rejected claims 1-10 and 12-20 under the judicially created doctrine of obviousness-type double-patenting over the claims of U.S. Patents 6,372,195, 6,258,339, 5,695,741, 5,639,443, 5,798,091, 5,804,162, and 6,193,952. In view of the current status of prosecution of the pending claims, Applicants are uncertain of the final scope of the claims of this application and respectfully request that the issue of double patenting be revisited after the claims are formally allowed.

Rejection under 35 U.S.C. §112, second paragraph.

The Examiner has rejected claim 16 under 35 U.S.C. §112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner suggests that since claim 16 depends on canceled claim 11, clarification of dependency is requested. Claim 16 has been amended to include the subject matter from previously canceled claim 11. This amendment obviates the rejection of claim 16 under 35 U.S.C. §112. Thus, Applicants respectfully request that this ground for rejection be withdrawn.

Rejections under 35 U.S.C. §102(b).

A) Rejection over Schneider.

The Examiner has rejected claims 1-10, 13-18, and 20 under 35 U.S.C. § 102(b) as anticipated by U.S. Patent 5,413,774 ("Schneider"). The Applicants respectfully traverse this ground for rejection.

The Examiner argues that Applicants' definition of the term "modifier gas" is all-inclusive and encompasses other gases such as oxygen, air, perfluorocyclooctane, perfluoropentane, perfluoroethane and perfluoromethane." (See May 3, 2005 Office Action at page 4.) The Examiner further asserts that the limitation "physiological gases surrounding external medium" such as blood, or "physiological gas present in the surrounding external medium" such as oxygen and air, recited in claims 3, 5-8, 10, 12-13, 17-19 are not viewed to positively limit the claimed microbubbles because they are not recited in a manner limiting the structural elements of the instantly claimed microbubbles. Applicants respectfully disagree with the Examiner's position. The specification specifically teaches that the term "modifier gas" is a gas that "must be capable of diluting and maintaining the gas osmotic agent or agents at a partial pressure below the vapor pressure of the gas osmotic agent or agents while the gases in blood or other surrounding liquid diffuse into the bubble." (See specification at page 11, paragraph 34.) The specification recites as follows:

> The present invention includes the discovery that a single gas or a combination of gases can together act to stabilize the structure of the microbubbles entraining or entrapping them. Essentially, the invention utilizes a first gas or gases (a "primary modifier gas") that optionally is ordinarily present in normal blood and serum in combination with one or more additional second gases (a "gas osmotic agent or agents" or a

"secondary gas") that act to regulate the osmotic pressure within the bubble. Through regulating the osmotic pressure of the bubble, the gas osmotic agent (defined herein as a single or mixture of chemical entities) exerts pressure within the bubble, aiding in preventing deflation. Optionally, the modifier gas may be a gas that is not ordinarily present in blood or serum. However, the modifier gas must be capable of diluting and maintaining the gas osmotic agent or agents at a partial pressure below the vapor pressure of the gas osmotic agent or agents while the gases in blood or other surrounding liquid diffuse into the bubble. In an aqueous medium, water vapor is not considered to be one of the "gases" in question. Similarly, when microbubbles are in a nonaqueous liquid medium, the vapor of that medium is not considered to be one of the "gases."

(See specification at page 11, paragraph 34.) The specification further recites as follows:

In a preferred embodiment, the microbubbles of the present invention have a surfactant-based bubble membrane. However, the principles of the invention can be applied to stabilize microbubbles of virtually any type. Thus, mixed gases or vapors of the type described above can stabilize albumin based bubbles, polysaccharide based microbubbles, spray dried microsphere derived microbubbles, and the like. This result is achieved through the entrapment, within the chosen microbubble, of a combination of gases, preferably a primary modifier gas or mixture of gases that will dilute a gas osmotic agent to a partial pressure less than the gas osmotic agent's vapor pressure until the modifier gas will exchange with gases normally present in the external medium. The gas osmotic agent or agents are generally relatively hydrophobic and relatively bubble membrane impermeable and also further possess the ability to develop gas osmotic pressures greater than 50, 75, or 100 Torr. In one preferred embodiment, the gas vapor pressure of the gas osmotic agent is preferably less than about 760 Torr at 37° C, preferably less than about 750, 740, 730, 720, 710, or 700 Torr, and in some embodiments less than about 650, 600, 500, or 400 Torr.

(See specification at page 15, paragraph 48.) The specification also recites as follows:

In preferred embodiments, the vapor pressure of the primary modifier gas is at least 660 Torr at 37° C. and the vapor pressure of the gas osmotic agent is at least 100 Torr at 37° C. For in vivo imaging mean bubble diameters between 1 and 10 μm are preferred, with 3 to 5 μm most preferred. The invention may in one embodiment also be described as a mixture of a first gas or gases and a second gas or gases within generally spherical membranes to form microbubbles, where the first gas and the second gas are respectively present in a molar ratio of about 1:100, 1:75, 1:50, 1:30, 1:20, or 1:10 to about 1000:1, 500:1, 250:1, 100:1, 75:1 or 50:1, and where the first gas has a vapor pressure of at least about (760-x)

mm Hg at 37° C, where x is the vapor pressure of the second gas at 37° C, and where the vapor pressure of each of the first and second gases is greater than about 75 or 100 mm Hg at 37° C.

(See specification at page 15, paragraph 49.) The specification also recites as follows:

> A major aspect of the present invention is in the selection of the gas phase. As was discussed above, the invention relies on the use of combinations of gases to harness or cause differentials in partial pressures and to generate gas osmotic pressures, which stabilize the bubbles. The primary modifier gas is preferably air or a gas present in air. Air and/or fractions thereof are also present in normal blood and serum. Where the microbubbles are to be used in an environment different from blood, the primary modifier gas is preferably selected from gases normally present in the external medium. Another criteria is the ease with which the primary modifier gas is diffused into or out of the bubbles. Typically, air and/or fractions thereof are also readily permeable through conventional flexible or rigid bubble surfaces. These criteria, in combination, allow for the rapid diffusion of the primary modifier gas into or out of the bubbles, as required.

(See specification at page 19, paragraph 60.) The specification also recites as follows:

> Modifier gases not present in the external medium can also be used. However, in this case the bubble will initially grow or shrink (depending on the relative permeability and concentrations of the external gases to the modifier) as the external gases replace the original modifier gas. If, during this process, the gas osmotic agent has not condensed, the bubble will remain stable.

(See specification at page 20, paragraph 61.)

In the present invention the mixed gases or vapors inside the microbubble stabilize the microbubble through entrapment within the chosen microbubble, of a combination of gases, preferably a primary modifier gas or mixture of gases that will dilute a gas osmotic agent to a partial pressure less than the gas osmotic agent's vapor pressure until the modifier gas will exchange with gases normally present in the external medium. Contrary to the Examiner's assertion, the "mere presence of any microbubbles in blood" is not sufficient to meet the limitations of the present invention. The osmotically stabilized microbubbles of Applicants' invention comprise a primary modifier gas or mixture of gases that dilute a gas osmotic agent to a partial pressure less than the gas osmotic agent's vapor pressure until the modifier gas will exchange with gases normally present in the external medium. Thus, contrary to the Examiner's

assertion not all microbubbles will be osmotically stabilized and not all gases can behave as a modifier gas.

The Examiner asserts that Schneider anticipates the limitations of the claimed microbubbles. The Examiner states that Schneider discloses microvesicles comprising a first gas selected from the group consisting of carbon dioxide, air, and oxygen, and a second gas selected from a group consisting of SF_6, SeF_6, CF_4, $CBrF_3$, C_4F_8, $CClF_3$, CCl_2F_2, C_2F_6, C_2ClF_5, $CBrClF_2$, C_2Cl2F_4, CBr_2F_2, and C_4F_{10}. The Applicants respectfully submit that Schneider does not anticipate currently amended claims 1-10, 13-18 and 20. Applicants claimed invention is directed to microbubbles according to the present invention comprise at least one fluorocarbon gas and at least one modifier gas in a certain molar ratio (between about 100:1 and about 1:1000). Schneider does not teach or suggest this claimed limitation.

Applicants respectfully note that Schneider does not disclose the ratios between the fluorocarbon compound and the initial gas. In fact, Schneider suggests that a complete removal of the initial gas is desirable, which is clearly inconsistent with the current invention. Schneider specifically states that the step of replacement of the initial gas by the replacement (the fluorocarbon) gas in the microbubbles "can be repeated once or more times to ensure complete replacement of the original gas by the new one." (See Schneider U.S. Patent col. 5,413,774 Col. 5, lns 16-18.) Schneider discloses replacing or substantially replacing a first gas with a second gas in its microvesicles. Even in those instances where Schneider's microvesicles contain a mixture of gases there is no disclosure of the ratios of such gas mixtures. Unlike Schneider, the microbubbles of the present invention comprise one fluorocarbon gas and at least one modifier gas in a molar ratio of between about 100:1 and about 1:1000. This ratio of gases within the microbubble maintains an internal osmotic pressure that is capable of counteracting the Laplace pressure produced by the surfactant surrounding the microbubble, thus stabilizing the microbubble.

The Applicants amended claims 1, 9, 10, 14, 17, 20. Claims 1, 10, and 17 are independent claims which now include additional limitations. Each of these claims now specifies the ratio between at least one fluorocarbon gas and at least one modifier gas. Accordingly, Schneider does not disclose every limitation of amended claims 1, 10, 17.

Claims 2-9 depend on claim 1 and thus incorporate every limitation of claim 1. Since Schneider does not anticipate the amended claim 1, Schneider does not anticipate claims 2-9. Claims 12-16 depend on claim 10 and thus incorporate each of the limitations of claim 10. Since Schneider does not anticipate the amended claim 10, Schneider does not anticipate claims 12-16. Claims 18-20 depend on claim 17 and thus incorporate each of the limitations of claim 1. Since Schneider does not anticipate the amended claim 17, Schneider does not anticipate claims 18-20.

Accordingly, the Applicants respectfully request that the Examiner withdraw this ground of rejection of claims 1-10, 13-18, and 20 on the basis of anticipation by Schneider.

B) Rejection over Lambert.

The Examiner has rejected claims 1-10 and 12-20 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent 5,552,133 ("Lambert"). The Applicants respectfully point out that Lambert is not a proper prior art reference for the present patent application because Lambert was filed on August 12, 1994, which is after the July 30, 1993 priority date of the present application. Furthermore, Lambert fails to teach or suggest the gas mixtures in molar ratios that are capable of stabilizing microbubbles, thus not meeting every limitation of the claims of the present application.

For these reasons, the Applicants respectfully request that the Examiner withdraw the rejection of claims 1-10 and 12-20 on the basis of anticipation by Lambert.

Rejections under 35 U.S.C. §103.

A) Rejection over Schneider in view of Tickner.

The Examiner has rejected claims 12 and 19 as unpatentable under 35 U.S.C. § 103 over Schneider in view of U.S. Patent 4,265,251 ("Tickner"). The Applicants respectfully traverse this rejection. First, the combination of Schneider and Tickner does not teach or suggest Applicants presently claimed invention. Second, Tickner teaches away from the current invention.

In order to establish a *prima facie* case of obviousness, the Examiner must show that

> there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP 2143.

The Examiner asserts that the only limitation not disclosed by Schneider is the use of oxygen as the modifier gas. (May 3, 2005 Office Action at page 6.) The Applicants respectfully disagree with this assertion. As discussed above, Schneider does not disclose or suggest the presently claimed molar ratios between the modifier gas and the fluorocarbon gas which are necessary to stabilize the microbubbles of the present invention. Accordingly, Schneider neither teaches nor suggests the presently claimed invention.

The Examiner states that Tickner teaches the use of oxygen in microbubbles for ultrasonic imaging. Id. at 6. Thus, the Examiner concludes that it would be obvious to a person skilled in the art to combine Schneider and Tickner. Id. at 7. The Examiner notes that Tickner suggests that freons, oxygen and nitrogen "are substantially interchangeable and are functional equivalents," thereby implying that a fluorocarbon gas is unnecessary. Id. Clearly, such teaching is inconsistent with and teaches away from the present invention, which clearly requires at least one fluorocarbon gas or vapor. In addition, the disclosures of Schneider and Tickner contradict each other. As stated above, Schneider suggests that it is preferable to eliminate the modifier gas completely and use only the fluorocarbon compound, thus implying that these two compounds are not functionally equivalent. (Schneider U.S. Patent 5,413,774 Col. 5, lns 16-18. Tickner suggests just the opposite. (Tickner U.S. Patent 4,265,251, Col 6, lns 62-67. Accordingly, Applicants respectfully suggest that Tickner and Schneider cannot be properly combined.

Even if Tickner and Schneider are combined, the resulting combination would not cure the deficiencies of Schneider, discussed above. Tickner does not disclose a mixture of at least two gases wherein at least one gas is a fluorocarbon. Tickner also does not teach the importance of molar ratios between the modifier gas and the fluorocarbon gas needed to keep the microbubbles of the present invention stabilized. Further, Tickner does not teach or suggest the use of perfluorocarbon compounds disclosed in the instant

application. While Tickner suggests the use of freons, this suggestion comes short of an enabling disclosure required for anticipation of the present invention. The Applicants respectfully point out that the term "freon" indicates "a variety of nonflammable gaseous or liquid fluorinated hydrocarbons employed primarily as working fluids in refrigeration and air conditioning and as aerosol propellants." (See The American Heritage® Dictionary of the English Language, Fourth Edition Copyright © 2000 by Houghton Mifflin Company.) Thus, Tickner discloses a broad genus. It is a well-settled law that a disclosure of a broad genus, such as freon, does not anticipate every species that makes up this genus if there is no motivation to select specific compounds claimed by the Applicant. (See MPEP 2144.08.) The Applicants respectfully submit that there is no teaching in Tickner that the perfluorocarbons disclosed by the Applicants would constitute a preferred group within the genus "freon." Accordingly, the combination of Schneider and Tickner does not teach or suggest every limitation of the present invention. Accordingly, the Applicants respectfully request that the Examiner withdraw the rejection of claims 12 and 19 over as unpatentable under 35 U.S.C. § 103 over Schneider in view of Tickner.

B) Rejection over Schneider in view of Unger.

The Examiner has also rejected claims 12 and 19 under 35 U.S.C. § 103 as unpatentable over Schneider in view of U.S. Patent 5,205,290 ("Unger"). The Applicants respectfully traverse this rejection. First, as discussed above, Schneider fails to teach or suggest the presently claimed invention. Second, Unger is not a reference from analogous prior art, and thus cannot be relied upon in making §103 rejection. Third, the combination of Schneider and Unger would not teach or suggest every limitation of the present invention.

A disclosure may only be used as a prior art reference for the purposes of rejection under 35 U.S.C. § 103 if it is from analogous prior art. (See MPEP 2141.01(a).) The Federal Circuit defined "analogous prior art" as a reference "either in the field of the Applicants' endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." (See MPEP 2141.01(a).) The Federal Circuit cautioned that it was "necessary to consider 'the reality of circumstances' – in other

words, common sense – in declaring in which fields a person of ordinary skill would reasonably expected to look for a solution to the problem facing the inventor." In re Oetiker, 977 F.2d 1443 (Fed. Cir. 1443, 1446) (quoting from In re Wood, 599 F.2d 1032, 1036 (C.C.P.A. 1979)).

In the decision in Wang Laboratories, Inc. v. Toshiba Corp., the Federal Circuit urged a narrow view of the analogous prior art, holding that a patent disclosing larger, more costly industrial memory compounds was not analogous prior art to a patent disclosing computer memory with minimum size, low cost, and easy reparability. 26 USPQ 2d 1767, 1773 (Fed. Cir. 1993).

In the instant case, the Examiner urges that microbubbles disclosed in Unger for the computer tomography images are within the analogous prior art for the present invention, which deals with ultrasound technology. (May 3, 2005 Office Action at page 8.) Applicants respectfully disagree with the Examiner's position because important differences exist between ultrasound imaging and computed tomography (CT).

Ultrasound imaging is based on the measurements of reflection of sound waves emitted by tested tissues. CT measures the radiodensity (electron density) of matter. Thus, ultrasound imaging and CT use different mechanisms of action. Clearly, measurements of radiodensity and measurements of sound waves are different techniques, and thus are in different fields.

Moreover, Applicants invention is directed to ultrasound contrast agents which have a relatively long useful life and which provide adequate sound wave reflection properties. It is not reasonable to assume that the skilled worker in the field of ultrasound imaging would venture into the field of computed tomography agents to mix and match components from the negative radiodense CT agents of Unger with the components from Scheidner's ultrasound contrast agents to produce the presently claimed microbubbles. Clearly, differences between CT and ultrasound imaging are greater than the differences between computer memory compounds discussed in the Wang Laboratories. Accordingly, Unger is not a proper prior art reference.

Furthermore, the microbubbles of the present invention grow and shrink to maintain osmotic equilibrium with the physiological gas saturation of the surrounding external medium. Thus, there is a great degree of flexibility in the microbubbles of the

present invention. In contrast, Unger discloses microspheres made of thermoplastic polymers, which form a rigid structure. For example, Unger notes that the microspheres of his invention can be filled by a vaporous liquid and expanded by heat. After the heat is removed, the microspheres "remain substantially fixed in their expanded position." U.S. Patent 5,205,290, col. 3, lns 53-56. Also see col. 4, lns 60-62 ("When heat is removed, the thermoplastic polymer retains at least some of its expanded shape.") Accordingly, Unger's microspheres maintain their shape not by regulation of osmotic equilibrium but through rigidity of their walls, and thus could hardly be considered true "bubbles".

The Examiner states that Unger "specifically teaches the use of perfluorocarbons such as those having between 1 and about 9 carbon atoms and between about 4 and about 20 fluorine atoms, especially C_4F_{10}." (May 3, 2005 Office Action at page 8.) In response, the Applicants respectfully point out that Unger discloses a wide variety of compounds which may be used for the heat expansion process in the preparation of the microspheres. Among those compounds are: "aliphatic hydrocarbons such as ethane, ethylene, propane, propene, butane, isobutane, neopentane, acetylene, hexane, heptane; chlorofluorocarbons, tetraalkyl silanes such as tetramethyl silane, trimethylethyl silane, trimethylisopropyl silane, and trimethyl n-propyl silane; as well as perfluorocarbons such as those having between 1 and about 9 carbon atoms and between about 4 and about 20 fluorine atoms, especially C_4F_{10}." (Unger U.S. Patent 5,205,290, Col. 4, lns 11-27.) Thus, Unger discloses a broad genus of volatile liquids which have vastly different properties. Unger does not teach or suggest that fluorocarbons have superior properties for increasing the useful life of his microspheres. Further, except for C_4F_{10}, Unger does not teach or suggest that the compounds disclosed by the Applicants are superior to the other members of the subgenus of perfluorocarbons. In fact, out of nine examples of Unger's disclosure, only one (Example 6) uses a pure perfluorocarbon, C_4F_{10} as the sole component in the void volume of the microsphere. Unger does not disclose Applicants' microbubbles comprising at least one fluorocarbon gas and at least one modifier gas in a molar ratio of between about 100:1 and about 1:1000. Thus, Unger does not teach or suggest the use of the compounds claimed in Applicants' invention. Accordingly,

Applicants respectfully request that the rejection for obviousness over Schneider in view of Unger be withdrawn.

Conclusion

In view of the foregoing amendments and remarks, the application is believed to be in condition for allowance, and early notice to this effect is earnestly solicited. If allowance of this application may be expedited by resolution of simple issues through a telephone conference, the Examiner is invited to call the undersigned.

Applicants hereby request a three-month extension of time in which to file this response. Thus, the $1,020.00 extension for response within the fifth month is being made by credit card payment. The required credit card payment form is attached. If any other fees are due, the USPTO is authorized to charge Deposit Account No. 50-3329.

Respectfully submitted,

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